eastern isotopes
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Dockets Management Branch (HFA-306),
Food and Drug Administration, Room 1-46 Park Building,
12420 Parklawn Drive,
Rockville, MD 20857.

Re: CDER, Generic Drugs. PET Drugs.

MODEL APPLICATION TO MANUFACTURE FLUDEOXYGLUCOSE F 18 INJECTION FOR MARKETING. Chemistry, Manufacturing, and Controls Section. Date: 9/20/99

Wednesday, October 06, 1999

Dear FDA Officer,

This is respectfully submitted as a comment on proposed regulation concerning CGMP regulations of PET drugs, namely Fludeoxyglucose F 18 and proposed model application for marketing of the above drug.

USP 19NF states:

> "2F03950
> FLUDEOXYGLUCOSE F 18 INJECTION
> ...
> RADIOCHEMICAL PURITY -- [NOTE -- The USP Fludeoxyglucose RS that is specified in this test is nonradioactive 2-deoxy-2-fluoro-D-glucose (formula weight 182.15)]. Apply a volume of the Injection appropriately diluted, such that it provides a count rate suitable for the radioactivity detection system being utilized, to an activated silica gel thin-layer chromatographic plate (see Chromatography <621>). Develop the chromatogram in a solvent system consisting of a mixture of acetonitrile and water (95:5) until the solvent has moved about three-fourths of the length of the plate. Allow the chromatogram to dry. Determine the radioactivity distribution by scanning the chromatogram with a suitable collimated radiation detector ... [standard solution test skipped - MK] ***The radioactivity of fludeoxyglucose F 18 is not less than 90% of the total radioactivity."***

The above stated limit of not less than 90% FDG implies that the balance of 10% may be represented by any other radioactive component, including of course the most common impurity F-18 fluoride. In proposed model application, there is an additional limit of not more than 2% of F-18 fluoride. In effect this represents lowering the limit for F-18 fluoride five fold – from 10% down to 2%. The limit may restrict usage of this invaluable tracer in clinical medicine.

Fludeoxyglucose F-18 is produced by PET centers and radiopharmaceutical companies for a number of years under USP limit of 90% RCP. The major radiochemical impurity is F-18 fluoride, which is also one of the raw materials used in the manufacturing process. All data published in the literature and used by the FDA to evaluate safety and effectiveness of FDG is collected using the drug manufactured under these specifications.

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10/7/99

99N-4063

It is also important to note that PET and coincidence scanners utilized for FDG imaging today are significantly different from those instruments that were used for F-18 Fluoride imaging 20 years ago. Any reference to recommended F-18 Fluoride doses in original NDA for bone imaging agent F-18 NaF is irrelevant to PET and coincidence imaging.

No limit on F-18 Fluoride impurity other than already established radiochemical purity of 90% FDG which allows up to 10% of unspecified radiochemical impurities is needed. Safety and effectiveness of FDG containing up to 90% of F-18 Fluoride has been demonstrated.

Furthermore, it is very important to understand that such limit, if imposed, will have serious implications on future development of PET imaging as a whole. To understand these implications we must consider sources of this impurity and methods to control its level.

There are two sources of F-18 Fluoride in the final product: 1-st the unreacted raw material, and 2-nd decomposition of the final product.

At the end of the manufacturing process the final product is filtered through the set of cartridges which effectively remove this impurity to about 1-2% level in most cases. Less than 1% of F-18 could be obtained if a larger cartridge with aluminum oxide is used. However, this unreacted F-18 Fluoride break through the aluminum cartridge is not the only and not the main source of this impurity in the final product.

The most significant source of F-18 Fluoride impurity in Fludeoxyglucose F-18 is radiolytic decomposition of the product during storage, transport, and use. In our experience, this process becomes noticeable when the concentration of FDG solution exceeds 50 mCi/ml in absence of stabilizers. Adding a stabilizer, such as ethanol or ascorbic acid to the final product controls the decomposition. However at concentrations over 100 mCi/ml even in presence of stabilizers the decomposition process increases concentration of free F-18 up to 4% as illustrated by typical stability test results discussed below.

Improvement in image quality, increase of patient comfort and reduction in exposure to workers is dependent on dose volume at the time of administration. Several facilities prefer volumes of less than 5 ml. Injecting over 5-ml doses presents significant challenges for imaging facilities. The ease of handling lower dose volumes could reduce misadministrations.

In our experience cost effective and reliable distribution of this product requires its production at least 12 hours prior to administration time, to allow flexibility in scheduling. Our studies show that an expiration time, greater then twelve (12) hours is possible. As an illustration, attached to this letter is the summary of radiochemical purity tests conducted at our facility as a part of stability studies. Complete results of stability tests are available upon request.

In recognition of the previously mentioned items, reasoning is established to produce F-18 Fludeoxyglucose in concentrations higher than specified for an RLD. In fact, at 40 mCi/ml at EOS a typical dose of 10 mCi will have a volume of 25 ml when administered 11 hours after release (12 hours after EOS) making it impractical to deliver and administer this dose. In our view, in order for PET imaging to become a clinically viable modality, it is absolutely essential that Fludeoxyglucose F-18 be manufactured in high concentrations for an extended delivery range. It is also important from regulatory point of view that manufacturing is conducted on a large scale, in which case cGMP standards may be applied more consistently and enforced more effectively. Otherwise, a cyclotron will be necessary in every large hospital and centralized nuclear pharmacy to support the expected demand of FDG. The result would be over 1000 - 2000 manufacturing sites, each producing very few doses per day. A higher concentration of FDG would allow 10 to 20 times fewer manufacturing sites to supply FDG.

The RLD volume concentration limit of 40 mCi/ml is based on a capacity limit of the 11 MeV cyclotron. The 11 MeV cyclotron is basically used for a research setting and the only type CTI manufactures. Several other vendors produce larger cyclotrons capable of making much higher concentrations of FDG. Currently, FDG produced by a CTI cyclotron has a very limited distribution to a local customers. Dose prices including shipping ranged from $650 to $1500 to support the local FDG production sites. Due to use of larger cyclotrons available from several vendors, pricing of FDG is possible at 25% to 50% of historic levels if a higher concentration is allowed. Affordable FDG creates an environment for patient access to this promising modality in the average hospital and clinic setting. Today, most institutions are entertaining the advantages of having PET imaging available, but high FDG pricing could keep this modality confined to large institutions. Setting a impurity of less than 2% gives CTI a competitive advantage over other vendors.

Our facility supplies over 40 customers in 12 states, delivering multiple doses per day. In order to do it, our company invested in a high production capacity cyclotron, and developed procedures and protocols that enable us to reliably and safely produce and dispense large number of patient doses per day.

We have thoroughly tested stability of the product in all respects including radiochemical purity and found that it meets all requirements of current USP, including 90% radiochemical purity, in concentrations up to 300 mCi/ml EOS.

In view of this consideration we respectfully ask to remove an additional limit on F-18 Fluoride impurity, and leave current USP limit of 90% FDG radiochemical purity. In case if the agency has data that show that FDG containing high amounts of Fluoride is not safe or effective, perhaps you might consider at least a higher limit that will not hinder commercialization of this useful drug. It appears that 5% on F-18 Fluoride would be achievable and reasonable, along with 90% overall radiochemical purity.

Please, contact me if you have any questions or if you require more detailed information. I can be reached at Tel. (703) 787 8010, Fax (703) 787 8011, e-mail maxim.kiselev@usa.net

Sincerely,

Maxim Kiselev, Ph.D.
Chemist
Eastern Isotopes, Inc.

ATTACHMENT:

Summary of RCP testing of Fludeoxyglucose F 18 Injection stability batches by Eastern Isotopes, Inc. July 1999

1. Sampling and storage.

Samples of the final drug product were taken at the end of production (EOS). The four 2 ml portions of the product were stored in either glass sterile vials supplied by Fujisawa USA (Deerfield IL), in an upright position, or disposable plastic syringes supplied by Becton Dickinson (Franklin Lakes NJ), in a plunger-up position with Luer port plugged with a sterile plastic plug. Each container type was tested in duplicate for each lot. Samples were stored at room temperature at 18-22 deg. C for more than 12 hours. Storage sample size was 2 ml for each container. QC samples were taken out of each container after 12 hours of storage for post expiration tests in the same manner as the QC sample for pre-release test.

2. Testing

Full QC testing with an exception of pyrogen and sterility tests was performed on samples after expiration. All tests were satisfactory at release and after expiration time. Only RCP test results are provided here. Other tests results are available upon request.

RCP tests were performed using USP method described above, with exception of use of standard solution. No standard solution was used, identification was done using Rf comparison to published and previously performed standard tests. The plates were scanned using Bioscan System 200 TLC scanner and analyzed using WinScan ver. 2.2 software. Percentages in the table represent respective peak count as a percentage of total plate counts with no correction for background.

Summary of TLC tests is provided in table below:

Lot	Concentration mCi/ml (EOS)	TLC At release		Container type	TLC After Expiration	
		%FDG	%Fluoride		%FDG	%Fluoride
071999T 2	263	96.5	none	vial	91.2	3.7
				vial	91.0	4.0
				syringe	91.9	3.4
				syringe	91.7	3.9
072099T 6	303	94.9	none	vial	91.7	3.3
				vial	91.3	3.5
				syringe	91.1	2.9
				syringe	90.9	2.1

All other tests results were satisfactory at release and expiration.

Evaluation - Method: QUICKST File: 071999T2.R01 User:

Sample No.:
Acquired: 19 Jul 1999 01:14

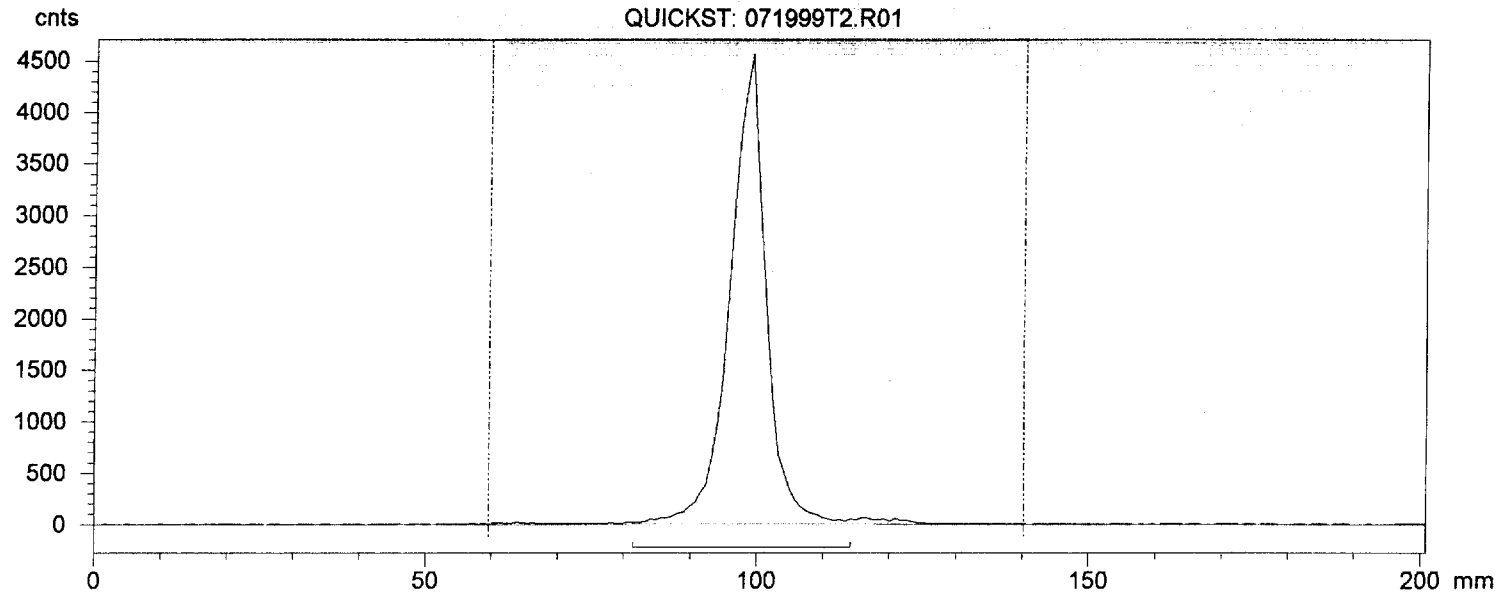
Sample Name:
Evaluated: 30 Sep 1999 22:11

Electronic Res: High | Bkgnd: None | Norm: None | Base Correct: On

Run Time: 0:09 | Total Counts: 35898 | Total CPM: 239320.0

Total count region: -5 mm - 200 mm

Name	Start (mm)	End (mm)	Max (mm)	RF	Region Counts	Region CPM	% of Total	% of ROIs
Rgn 2	81.5	114.2	99.1	0.490	34650	231000.0	96.52	100.00
1 Peak					34650	231000.0	96.52	100.00



lot 071999T2 at release

Sample No.:
Acquired: 19 Jul 1999 21:12

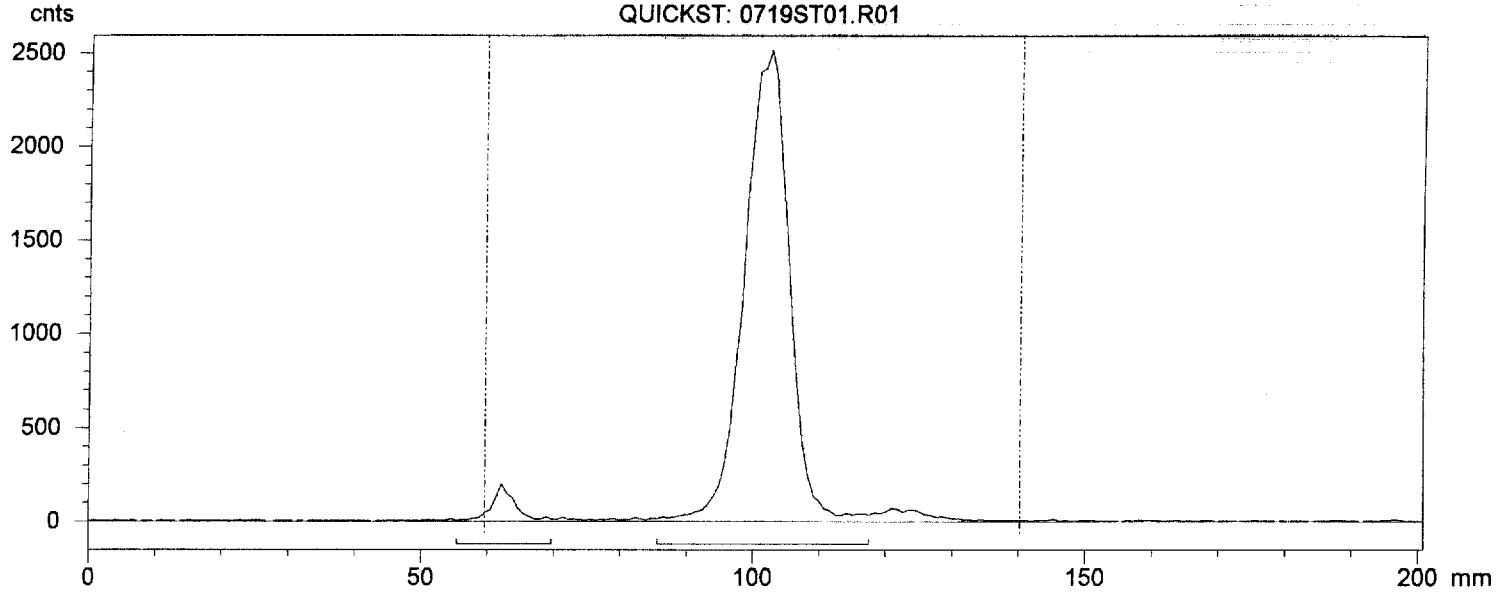
Sample Name:
Evaluated: 30 Sep 1999 22:11

Electronic Res: High | Bkgnd: None | Norm: None | Base Correct: On

Run Time: 5:00 | Total Counts: 25843 | Total CPM: 5168.6

Total count region: -5 mm - 200 mm

Name	Start (mm)	End (mm)	Max (mm)	RF	Region Counts	Region CPM	% of Total	% of ROIs
Rgn 1	55.4	69.7	62.2	0.031	946	189.2	3.66	3.86
Rgn 2	85.7	117.6	102.5	0.531	23558	4711.6	91.16	96.14
2 Peaks					24504	4900.8	94.82	100.00



Sample No.:
Acquired: 19 Jul 1999 21:07

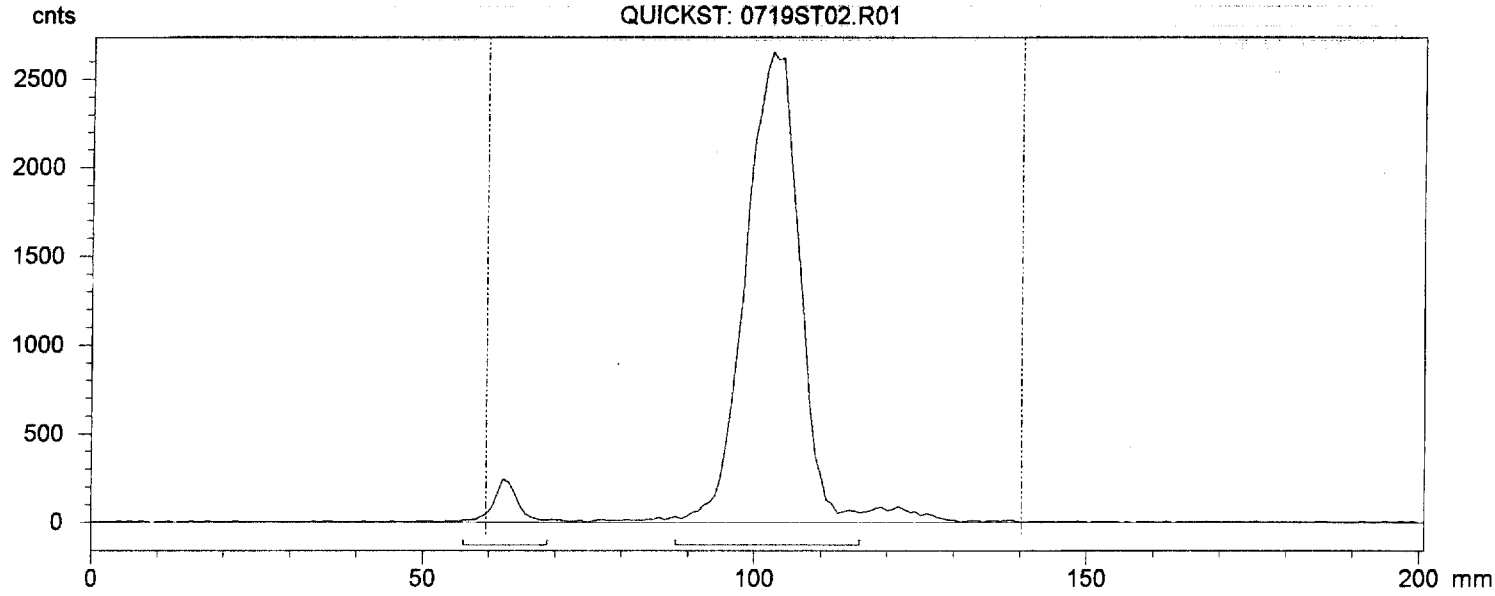
Sample Name:
Evaluated: 30 Sep 1999 22:11

Electronic Res: High | Bkgnd: None | Norm: None | Base Correct: On

Run Time: 4:47 | Total Counts: 32300 | Total CPM: 6752.6

Total count region: -5 mm - 200 mm

Name	Start (mm)	End (mm)	Max (mm)	RF	Region Counts	Region CPM	% of Total	% of ROIs
Rgn 1	56. 3	68. 9	62. 2	0. 031	1219	254. 8	3. 77	3. 98
Rgn 2	88. 2	115. 9	102. 5	0. 531	29396	6145. 5	91. 01	96. 02
2 Peaks					30615	6400. 3	94. 78	100. 00



Evaluation - Method: QUICKST File: 0719ST03.R01 User:

Sample No.:
Acquired: 19 Jul 1999 21:02

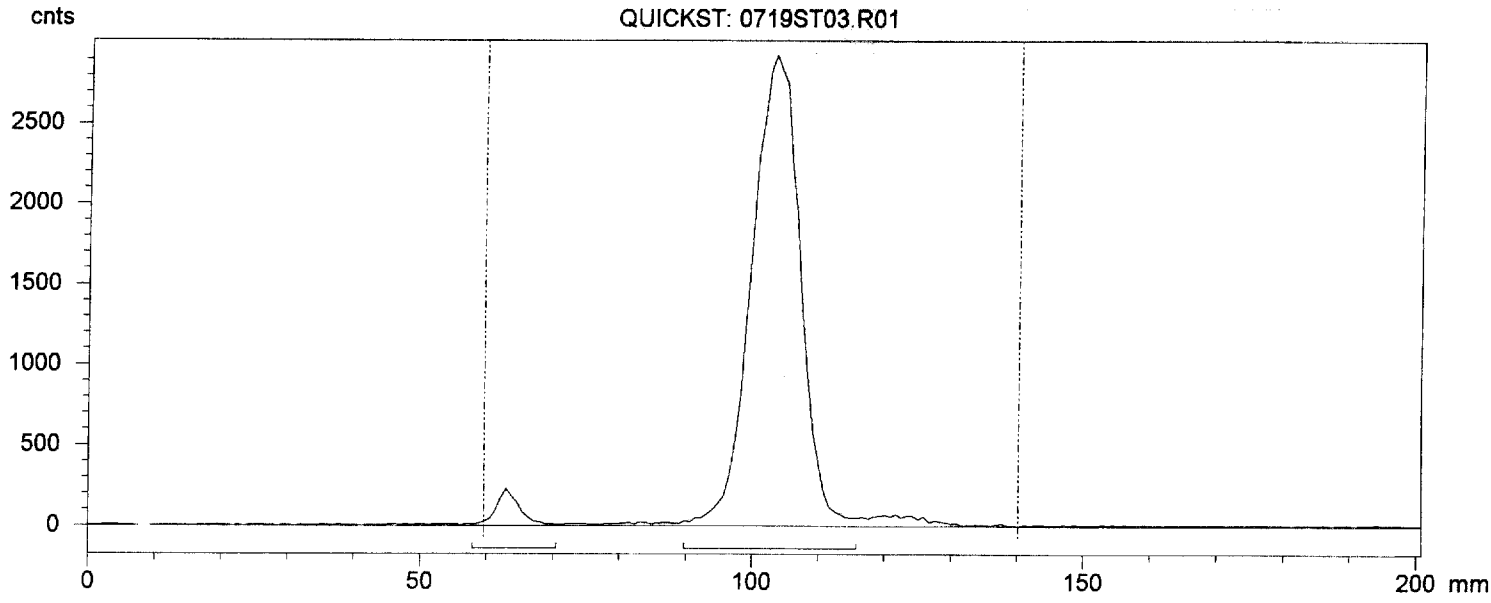
Sample Name:
Evaluated: 30 Sep 1999 22:11

Electronic Res: High | Bkgnd: None | Norm: None | Base Correct: On

Run Time: 3:58 | Total Counts: 32214 | Total CPM: 8121.2

Total count region: -5 mm - 200 mm

Name	Start (mm)	End (mm)	Max (mm)	RF	Region Counts	Region CPM	% of Total	% of ROIs
Rgn 1	58. 0	70. 6	63. 0	0. 042	1093	275. 5	3. 39	3. 56
Rgn 2	89. 9	115. 9	103. 3	0. 542	29593	7460. 4	91. 86	96. 44
2 Peaks					30686	7736. 0	95. 26	100. 00



Sample No.:
Acquired: 19 Jul 1999 20:58

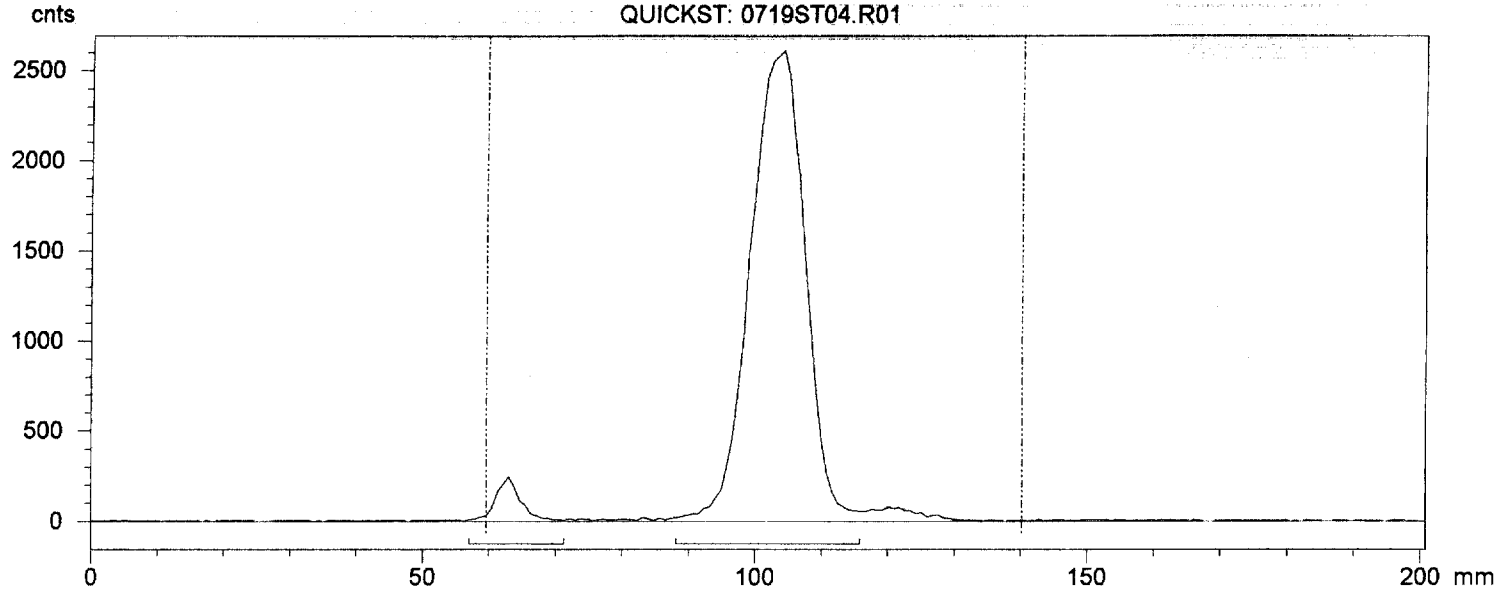
Sample Name:
Evaluated: 30 Sep 1999 22:11

Electronic Res: High | Bkgnd: None | Norm: None | Base Correct: On

Run Time: 3:35 | Total Counts: 32381 | Total CPM: 9036.6

Total count region: -5 mm - 200 mm

Name	Start (mm)	End (mm)	Max (mm)	RF	Region Counts	Region CPM	% of Total	% of ROIs
Rgn 1	57.1	71.4	63.0	0.042	1278	356.7	3.95	4.13
Rgn 2	88.2	115.9	104.2	0.552	29691	8285.9	91.69	95.87
2 Peaks					30969	8642.5	95.64	100.00



Evaluation - Method: QUICKST File: 072099T6.R01 User:

Sample No.:
Acquired: 20 Jul 1999 07:31

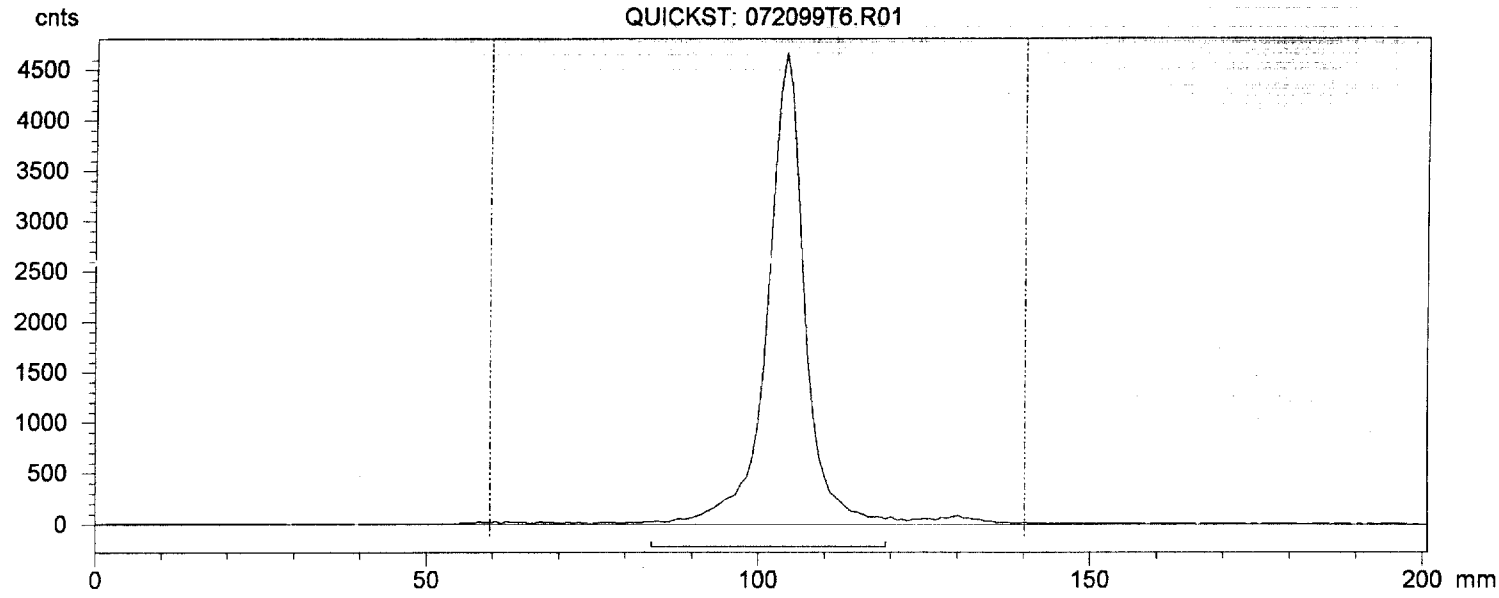
Sample Name:
Evaluated: 30 Sep 1999 22:18

Electronic Res: High | Bkgnd: None | Norm: None | Base Correct: On

Run Time: 0:09 | Total Counts: 38235 | Total CPM: 254900.0

Total count region: -5 mm - 200 mm

Name	Start (mm)	End (mm)	Max (mm)	RF	Region Counts	Region CPM	% of Total	% of ROIs
Rgn 2	84.0	119.3	104.2	0.552	36279	241860.0	94.88	100.00
1 Peak					36279	241860.0	94.88	100.00



lot 072099T6 at release

Evaluation - Method: QUICKST File: 0720ST01.R01 User:

Sample No.:
Acquired: 20 Jul 1999 23:15

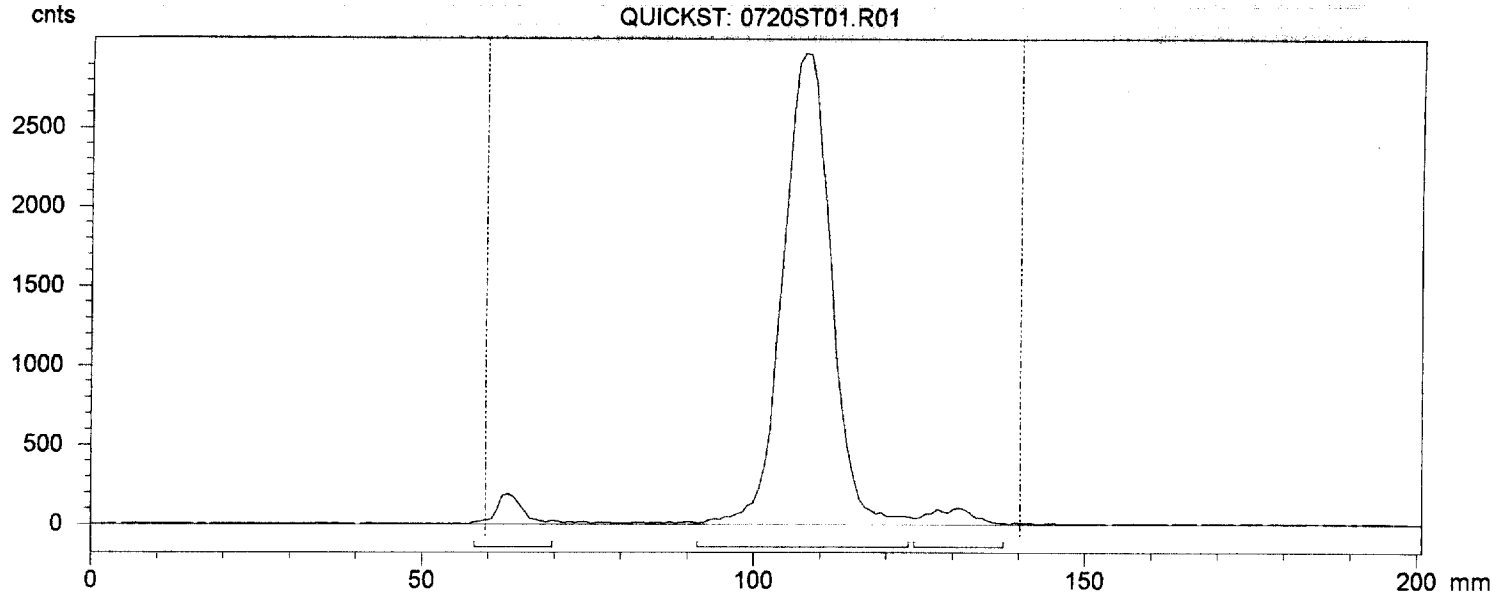
Sample Name:
Evaluated: 30 Sep 1999 22:18

Electronic Res: High | Bkgnd: None | Norm: None | Base Correct: On

Run Time: 1:47 | Total Counts: 32523 | Total CPM: 18237.2

Total count region: -5 mm - 200 mm

Name	Start (mm)	End (mm)	Max (mm)	RF	Region Counts	Region CPM	% of Total	% of ROIs
Rgn 1	58.0	69.7	63.0	0.042	1041	583.7	3.20	3.27
Rgn 2	91.6	123.5	107.5	0.594	29832	16728.2	91.73	93.69
Rgn 3	124.3	137.8	131.0	0.885	967	542.2	2.97	3.04
3 Peaks					31840	17854.2	97.90	100.00



Sample No.:
Acquired: 20 Jul 1999 23:12

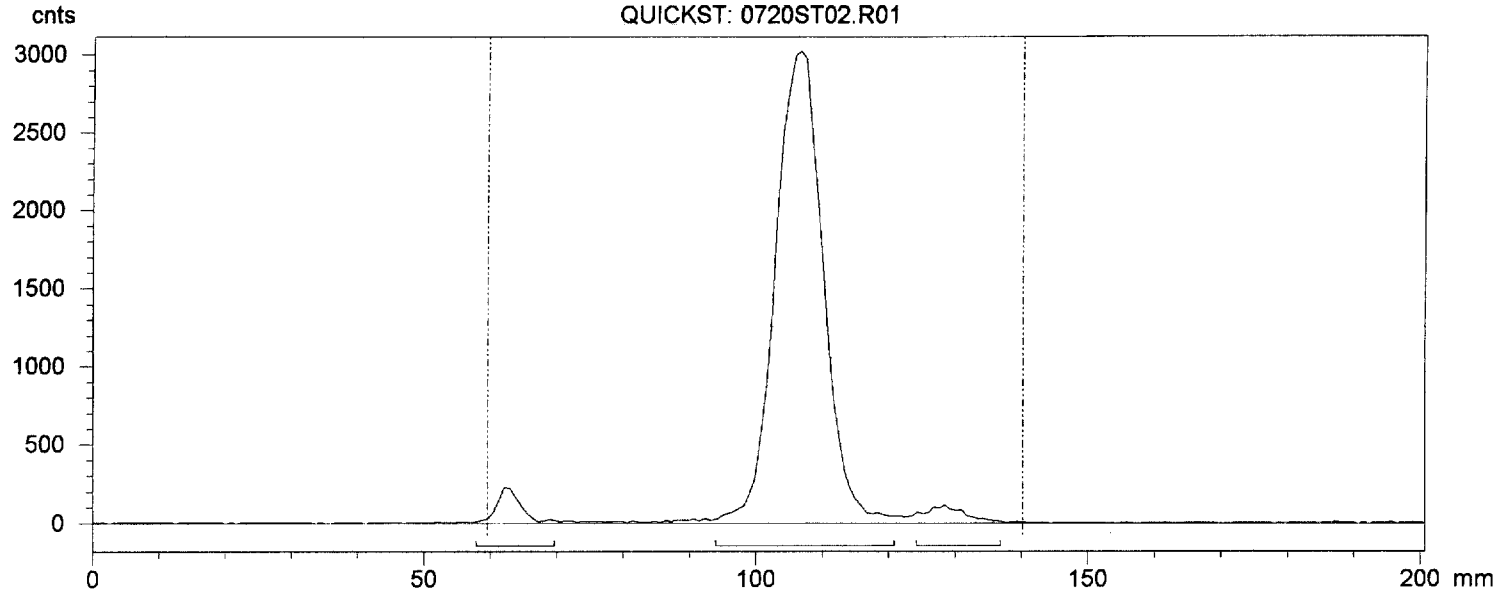
Sample Name:
Evaluated: 30 Sep 1999 22:18

Electronic Res: High | Bkgnd: None | Norm: None | Base Correct: On

Run Time: 1:47 | Total Counts: 32953 | Total CPM: 18478.3

Total count region: -5 mm - 200 mm

Name	Start (mm)	End (mm)	Max (mm)	RF	Region Counts	Region CPM	% of Total	% of ROIs
Rgn 1	58.0	69.7	62.2	0.031	1153	646.5	3.50	3.59
Rgn 2	94.1	121.0	106.7	0.583	30086	16870.7	91.30	93.57
Rgn 3	124.3	136.9	128.5	0.854	915	513.1	2.78	2.85
3 Peaks					32154	18030.3	97.58	100.00



Sample No.:
Acquired: 20 Jul 1999 23:10

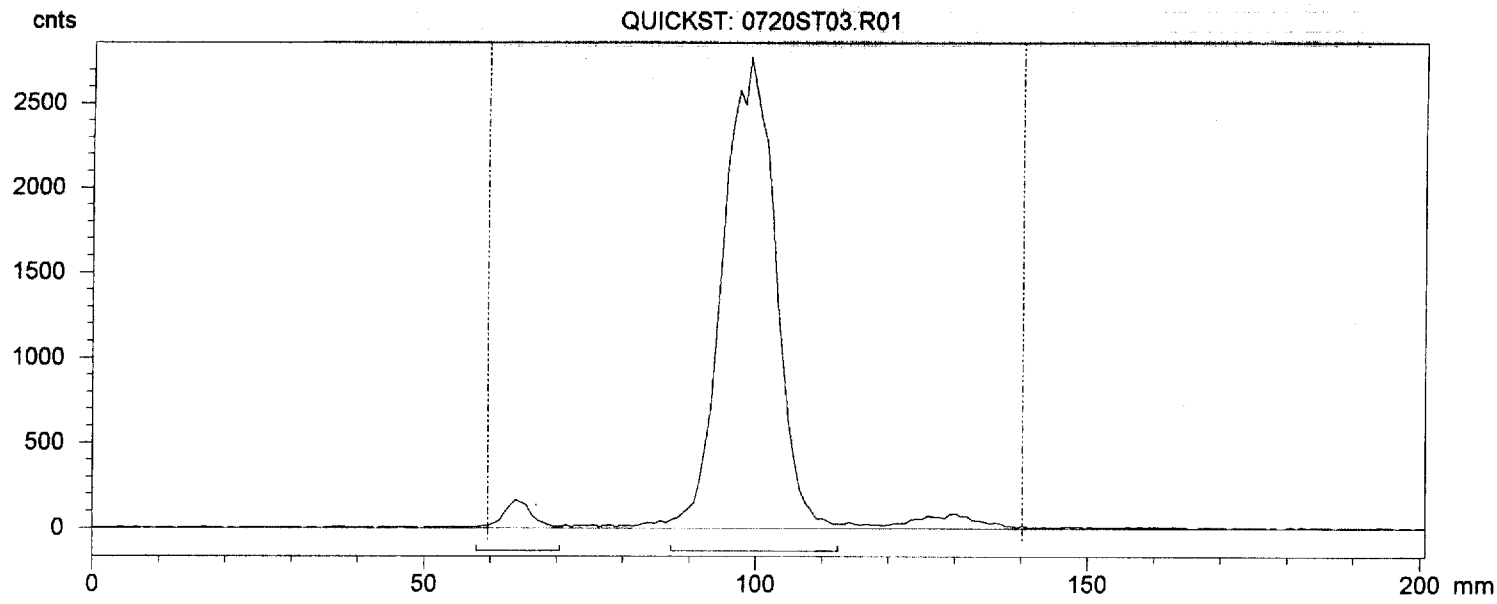
Sample Name:
Evaluated: 30 Sep 1999 22:18

Electronic Res: High | Bkgnd: None | Norm: None | Base Correct: On

Run Time: 1:58 | Total Counts: 33083 | Total CPM: 16821.9

Total count region: -5 mm - 200 mm

Name	Start (mm)	End (mm)	Max (mm)	RF	Region Counts	Region CPM	% of Total	% of ROIs
Rgn 1	58.0	70.6	63.8	0.052	948	482.0	2.87	3.05
Rgn 2	87.4	112.6	99.1	0.490	30131	15320.8	91.08	96.95
2 Peaks					31079	15802.9	93.94	100.00



Sample No.:
Acquired: 20 Jul 1999 23:06

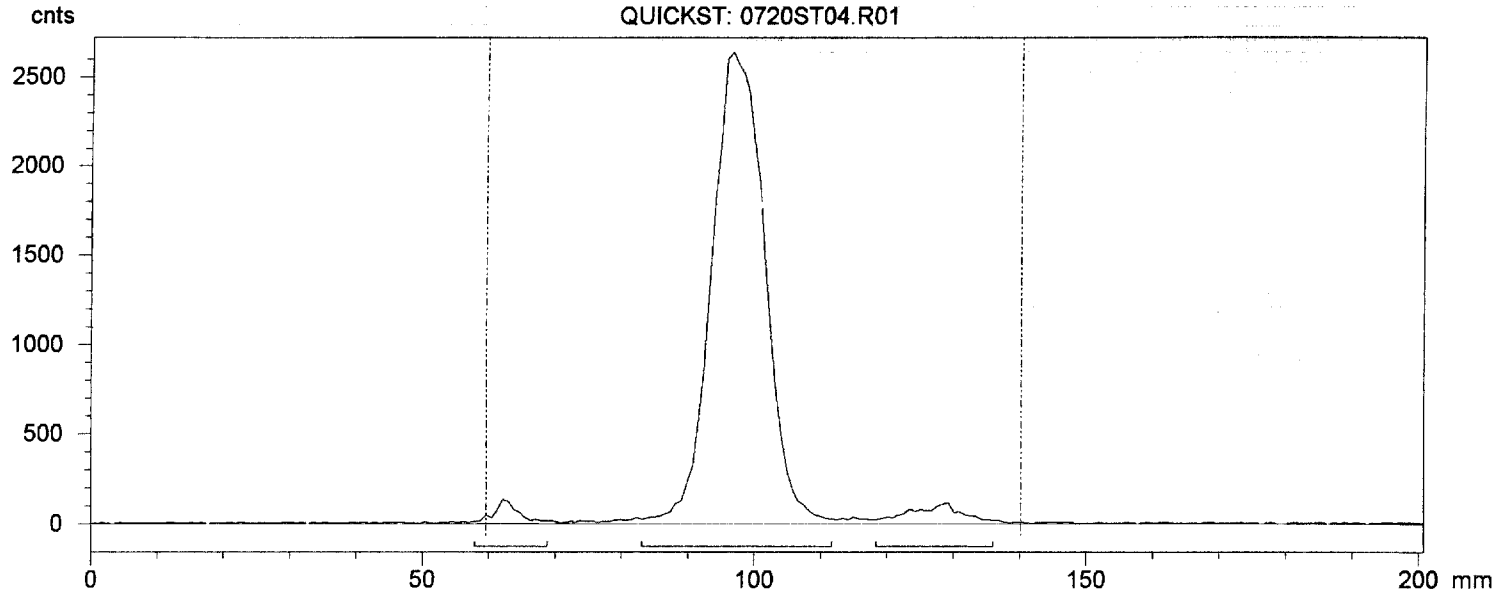
Sample Name:
Evaluated: 30 Sep 1999 22:18

Electronic Res: High | Bkgnd: None | Norm: None | Base Correct: On

Run Time: 3:16 | Total Counts: 32056 | Total CPM: 9813.1

Total count region: -5 mm - 200 mm

Name	Start (mm)	End (mm)	Max (mm)	RF	Region Counts	Region CPM	% of Total	% of ROIs
Rgn 1	58.0	68.9	62.2	0.031	684	209.4	2.13	2.20
Rgn 2	83.2	111.7	96.6	0.458	29128	8916.7	90.87	93.83
Rgn 3	118.4	136.1	129.4	0.865	1230	376.5	3.84	3.96
3 Peaks					31042	9502.7	96.84	100.00



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